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| 10/723,520 | 11/26/2003 | Mark R. Andersen | A-71902/AMP/JFB | 8934 |

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| EXAMINER | |
|---|---|
| PANDE, SUCHIRA | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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| 3 MONTHS | 01/19/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 10/723,520 | ANDERSEN ET AL. |
| | Examiner | Art Unit |
| | Suchira Pande | 1637 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *10-18 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,19-35 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/22/04,1/14/05,7/28/06*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20061018*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of species i. real time polymerase chain reaction amplification; v. 5'exonuclease probes; and xi. gene expression analysis, in the reply filed on 29 November, 2006 is acknowledged. Accordingly claims 1-9,19-35, and 37-43 that read on the elected species are being examined in this action.

### *Specification*

2. The disclosure is objected to because of the following informalities: Page 2, line 5 contains a blank. Application number and filing date of the appropriate priority document needs to be filled in.

Appropriate correction is required.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See pages 15, 20 and 31 for example. Applicant is required to scan the entire application and delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. The use of numerous trademarks such as TAQMAN®, MOLECULAR BEACONS™, SUNRISE® etc. have been noted in this application. See page 4 for example. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent

their use in any manner, which might adversely affect their validity as trademarks.

Applicant is advised to scan the entire application and make appropriate corrections.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The claims recite a percentage of 70% and 90% respectively. But claims as recited fail to specify percentage of what! Hence it is unclear to one of ordinary skill in the art what is being claimed.

7. Claims 31 and 42 contain the trademark/trade name SYBR® green I. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an intercalating and a minor groove binding dye and, accordingly, the identification/description is indefinite.

***Claim Interpretation***

8. Claims 22 and 23, are indefinite as pointed out above. In view of compact prosecution policy of the office, for examination purposes Examiner is interpreting the claim to mean any desired expression level can be set as zero percent or 100% and then a number specified that is greater than zero percent or less than 100% as the cut off value. Expression of genes that are above or below that cut off will result in identification of genes whose expression is higher or lower than the specified cut off expression level.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-2, 4-9, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Heid et al. (1996) Genome Research 6: 986-994.

Regarding claim 1, Heid et al. teach : A method for quantifying the expression of target gene sequences of interest in a sample (see title and whole article), comprising the steps of:

(i) amplifying one or more cDNA molecules derived from a sample by polymerase chain reaction in the presence of a plurality of amplification primer sets suitable for amplifying target gene sequence of interest (see page 993 par. 2 section Amplification of Target DNA and detection of Amplicon factor VIII),

and in the presence of at least one oligonucleotide probe complementary to a region of an amplified target gene sequence( see page 987 par. 3 where hybridization probe is taught) ,

said at least one oligonucleotide probe optionally labeled with a labeling system suitable for monitoring the amplification reaction as a function of time (see page 987 par. 3 where real time monitoring-- monitoring the amplification reaction as a function of time—using dual –labeled fluorogenic hybridization probe labeled with FAM and TAMRA is taught), and

(ii) quantifying the target gene sequences amplified in step (i) (see page 987 par. 4 results section).

Thus Heid et al teach all elements of claim 1.

Regarding claim 2, Heid et al. teaches a method in which the amplification of step (i) is further carried out in the presence of a reverse transcriptase such that the polymerase chain reaction is reverse-transcription polymerase chain reaction and wherein the one or more cDNA molecules is obtained from mRNA derived from the sample (see page 986 par. 2-3 where reverse transcriptase RT-PCR is taught) .

Regarding claim 4, Heid et al. teaches a method in which said quantifying comprises analysis by real-time polymerase chain reaction amplification (see page 986 abstract line 1).

Regarding claim 5, Heid et al. teaches a method in which the polymerase chain reaction of step (i) is carried out for a number of cycles such that the amplification

remains in the linear range (see page 988 figure 1 panel A where amplification in linear range is taught).

Regarding claim 6, Heid et al. teaches a method in which the amplification in step (i) is achieved with a thermostable DNA polymerase (see page 993 par. 3 where thermostable Taq DNA polymerase is taught).

Regarding claims 7 & 8, Heid et al. teaches a method in which said at least one oligonucleotide probe is labeled with a moiety capable of producing a detectable signal (see page 987 par. 3 where FAM a fluorophore is taught as label capable of producing a detectable signal).

Regarding claim 9, Heid et al. teaches a method in which said at least one oligonucleotide probe is 5'-exonuclease probes (see page 987 par. 3-4 where 5'-Taqman exonuclease probes that are based on 5' nuclease activity of Taq polymerase are taught).

Regarding claim 43, Heid et al. teaches method of a claims 1 in which the amplification is carried out in the presence of uracil N-glycosylase (see page 993 par. 3 where AmpErase uracil N-glycosylase is taught).

11. Claims 1-4,19-28, 32-35 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Dolganov et al. (2001) Genome Research 11:1473-1483.

Regarding claim 1, Dolganov et al. teaches a method for quantifying the expression of target gene sequences of interest in a sample (see page 1473, par. 2 where real time PCR quantification is taught), comprising the steps of:

(i) amplifying one or more cDNA molecules derived from a sample by polymerase chain reaction in the presence of a plurality of amplification primer sets suitable for amplifying target gene sequence of interest, and in the presence of at least one oligonucleotide probe complementary to a region of an amplified target gene sequence, said at least one oligonucleotide probe optionally labeled with a labeling system suitable for monitoring the amplification reaction as a function of time (see page 1474, par. 1 and Fig. 1 where RT-PCR for 34 genes was performed. Taqman hybridization probe is taught here which inherently indicates that it is complementary to a region of an amplified target gene sequence. Taqman probe has fluorescein reporter dye at 5' end (FAM)).

(ii) quantifying the target gene sequences amplified in step (i) (Gene quantification via real time PCR using nested Taqman primers is taught see legend of fig. 1) .

Thus Dolganov et al teach all elements of claim 1.

Regarding claim 19, Dolganov et al. teaches a method for determining a gene expression profile in a sample (see title), comprising the steps of:

(i) amplifying one or more cDNA molecules (see page 1473 abstract where expression of 75 genes is measured) derived from said sample (from bronchial biopsy sample) by polymerase chain reaction in the presence of a plurality of amplification primer sets suitable for amplifying target gene sequences of interest (see page 1473 par. 1 where multiplex PCR typically with a mix of 100-300 gene specific primers is taught);

(ii) identifying amplified target gene sequences having an observed efficiency of amplification greater than a selected level (see figs. 2 & 3 where amplification above a chosen threshold $C_T$ is taught); and

(iii) quantifying the target gene sequences identified in step (ii) to obtain a gene expression profile (see page 1474 par. 1 and Fig. 1 where transcriptional profiling for 34 genes of varying abundance was performed using RT-PCR).

Thus Dolganov et al. teaches all elements of claim 19.

Regarding claim 33, Dolganov et al. teaches a method of generating a plurality of target sequences of interest, comprising the step of: amplifying by polymerase chain reaction one or more target polynucleotide in the presence of a plurality of amplification primers suitable for amplifying target sequences of interest and in the presence of at least one oligonucleotide probe complementary to a region of an amplified target sequence of interest, said oligonucleotide probe being optionally labeled with a labeling system suitable for monitoring an amplification reaction as a function of time (see above where this is described in detail while discussing claim 1).

Regarding claims 2 & 20, Dolganov et al. teaches generating RT-PCR for 34 genes as described above for claims 1&19 therefore it inherently teaches a method in which the amplification of step (i) is further carried out in the presence of a reverse transcriptase such that the polymerase chain reaction is reverse-transcription polymerase chain reaction and wherein the one or more cDNA molecules is obtained from mRNA derived from the sample.

Regarding claims 3 & 21, Dolganov et al. teaches a method in which the one or more cDNA molecules comprise a cDNA library (see page 1474 where 34 genes of varying abundance in the sample were reverse transcribed and the RT-PCR products were cloned into pCRII-TOPO vector is taught. Thus Dolganov et al. teaches a cDNA library).

Regarding claims 22 & 23, Dolganov et al. teaches a method in which relative transcript number of 75 genes from Asthmatic patients were compared to the healthy subjects as shown in page 1478-1479 Table 2, a huge range of expression levels are determined ranging from as high as 40 fold to as low as 0.223. These comparisons are based on the expression levels of same gene in the two subject populations. However, expression level of any given gene can be chosen as a base line and genes with expression level above that or below that cut off percentage can be determined. Thus Dolganov et al. teaches any selected range can be chosen as a cutoff. Thereby Dolganov et al. teaches selected level is 70% (claim 22) and selected level is 90% (claim 23).

Regarding claims 4 & 24, Dolganov et al. teaches said quantifying comprises analysis by real-time polymerase chain reaction amplification (see page 1473 abstract where gene quantification via real-time PCR-based method is taught).

Regarding claims 25 and 34, Dolganov et al. teaches a method in which the amplifying in step (i) is further carried out in the presence of an oligonucleotide probe complementary to a region of an amplified target gene sequence of interest, said probe being labeled with a labeling system suitable for monitoring the amplification reaction in

step (i) as a function of time (see page 1474, par. 1 and Fig. 1 where RT-PCR for 34 genes was performed. Taqman hybridization probe is taught here which inherently indicates that it is complementary to a region of an amplified target gene sequence. Taqman probe has fluorescein reporter dye at 5' end (FAM) which is suitable for real time detection see legend of fig. 1).

Regarding claim 26, Dolganov et al. teaches a method in which the product of step (i) is divided into a plurality of aliquots and said quantifying in step (ii) is performed on said aliquots (see page 1474 par. 2).

Regarding claim 27, Dolganov et al. teaches a method in which step (ii) comprises amplifying the product in one or more separate aliquots by polymerase chain reaction in the presence of an amplification primer set suitable for amplifying one of the target sequences of the plurality (see page 1474 par. 2 and fig. 1 where multiplex RT-PCR is followed by real time PCR using nested primers on small aliquots of RT-PCR product is taught).

Regarding claim 28, Dolganov et al. teaches a method in which the sequences of the amplification primer sets of step (i) are the same as the sequences of the amplification primer sets of step (ii) (see page 1475, par. 2 and Fig. 4 where GAPDH, interleukin IL-8 and IL-13 were quantified is step 1 gene specific primer sets are taught for RT PCR amplification and then aliquots of the cDNA produced were quantified by real time amplification using primers specific for the above 3 genes. No explicit statement is made that same primers were used but this teaching by Dolganov et al. indicates that same primer sets could certainly be used both of step (i) and (ii).

Regarding claim 32, Dolganov et al. teaches a method in which the polymerase chain reaction of step (i) is carried out for a number of cycles such that the amplification remains in the linear range (see page 1474 par. 3 bottom and fig. 2 and 3 where linear amplification is taught up to 25 cycles for most abundant message and 30 cycles for less abundant message).

Regarding claim 35, Dolganov et al. teaches a method in which the product of the amplification is further subjected to gene expression analysis (see page 1476 par. 2-page 1477 par. 1-2 where gene expression analysis of 75 genes is taught).

Regarding claim 37, Dolganov et al. teaches a method in which the product of the amplification is divided into a plurality of aliquots (see page 1474 par. 2).

Regarding claim 38, Dolganov et al. teaches a method in which the product of the amplification is divided into a plurality of aliquots and wherein said at least one assay is performed on at least one of said aliquots. (see page 1474 par. 2 and page 1475 par. 1 where gene expression analysis is performed on at least one aliquot).

Regarding claim 39, Dolganov et al. teaches wherein the number of aliquots is equal to the number of primer pairs used in said amplifying (see page 1475 par. 2 and Fig. 4 where gene expression of 6 genes of varying abundance is taught here the number aliquots is equal to the number of primer pairs (6 primer pairs, one pair specific for each gene to be studied) used in said amplifying).

***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 29-31, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dolganov et al. (2001) Genome Research 11:1473-1483 as applied to claims 1-4 and 19-28 above in view of Heid et al. (1996) Genome Research 6: 986-994 as applied to claims 1-2 and 4-9 above.

Regarding claim 29, Dolganov et. al. teaches the method of claim 27 suitable for monitoring the amplification reaction as a function of time.

Regarding claim 40, Dolganov et. al. teaches a method of generating a plurality of different target sequences of interest, comprising the step of: amplifying by polymerase chain reaction one or more target polynucleotide in the presence of a plurality of amplification primers suitable for amplifying target sequences of interest thereby generating a plurality of target sequences of interest (see fig. 1 and page 1474 par. 2) .

Regarding claim 29, Dolganov et. al. does not teach a method in which the amplifying in step (ii) is further carried out in the presence of a molecule that produces a detectable signal when bound to a double-stranded polynucleotide suitable for monitoring the amplification reaction as a function of time.

Regarding claim 40, Dolganov et. al. does not teach a molecule that produces a detectable signal when bound to a double-stranded polynucleotide, said molecule suitable for monitoring the amplification reaction as a function of time.

Regarding claims 29 and 40, Heid et al. teaches a method in which the amplifying in step (ii) is further carried out in the presence of a molecule that produces a detectable signal when bound to a double-stranded polynucleotide suitable for monitoring the amplification reaction as a function of time (see Heid et al. page 992 where intercalating dye ethidium bromide is taught as a molecule that produces a detectable signal when bound to a double-stranded polynucleotide suitable for monitoring the amplification reaction as a function of time).

Regarding claims 30 & 41, Heid et al. teaches a method in which the molecule is selected from the group consisting of an intercalating dye and a minor groove binding dye (see Heid et al. page 992 where intercalating dye ethidium bromide is taught as a molecule).

Regarding claims 31 & 42, Heid et al. teaches a method in which the molecule is ethidium bromide (see claims 29 and 30 above).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Heid et al. in the method of

Dolganov et al. The motivation to do so is provided by Heid et al. who state " we have developed a novel " real time" quantitative PCR method. The method measures PCR product accumulation through a dual-labeled fluorogenic probe (i.e., Taq Man Probe). This method provides very accurate and reproducible quantitation of gene copies. Unlike other quantitative PCR methods, real time PCR does not require post-PCR sample handling, preventing potential PCR product carry-over contamination and resulting in much faster and higher throughput assays (see abstract)."

***Conclusion***

All claims under examination 1-9, 19-35 and 37-43 are rejected over prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
1/5/07